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(21) International Application Number: PCT/US99/23153 (22) International Filing Date: 6 October 1999 (06.10.99) (30) Priority Data: 60/104,141 14 October 1998 (14.10.98) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventors: LIU, Song; 9338 Ambleside Drive, Cincinnati, OH 45241 (US); PORTLOCK, David, Edward; 3237 Chestnut Landing Drive, Maineville, OH 45039 (US). PONG, Schwe, Fang; 8005 Tylers Way, West Chester, OH 45069 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).		(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
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<div style="text-align: center;"> </div>		
(57) Abstract		
<p>The subject invention involves compounds having the structure: (1) wherein the C_α-N_β, C₅-C₆, and C₆-C₇ bonds are each single or double bonds, except that both C₅-C₆ and C₆-C₇ are double bonds; R₁ is selected from hydrogen, alkyl, aryl, and heterocycle; R₂ - R₁₅ are independently selected from hydrogen and other substituents; and pharmaceutically-acceptable forms thereof. The subject invention also involves pharmaceutical compositions containing such compounds, and methods for treating or preventing diseases and disorders using such compounds.</p>		

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IMIDAZO-BENZAZEPINES HAVING CARDIOVASCULAR, ANTITUMOR, ANTIINFECTIVE AND ANTIINFLAMMATORY ACTIVITY

5

FIELD OF THE INVENTION

10 The subject invention relates to novel N-phenylmethyl-5,6-dihydro-imidazo[5,1-a]benzazepin-3-amine compounds, pharmaceutical compositions containing them, and their therapeutic or preventative use in the areas of cardiovascular, oncology, infectious and inflammatory diseases.

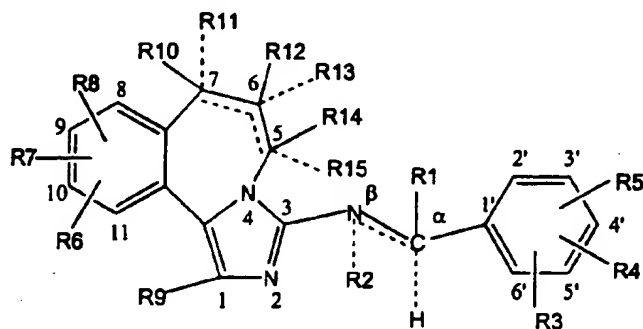
BACKGROUND

15 Certain imidazo-isoquinoline compounds are disclosed in U.S. Patent No. 3,917,610 issued November 4, 1975; they are reported to have certain cardiovascular activities. One such compound is further reported on in Borchard, Fox, and Greeff, "The Positive Inotropic, Antiarrhythmic and Na^+ , K^+ -ATPase Inhibitory Effects of the Isoquinoline Derivative, BIIA", *Achives of Pharmacology*, vol. 312 (1980), pp. 187-192.

20

SUMMARY OF THE INVENTION

The subject invention includes compounds having the structure:



wherein:

- (a) The bond between C_α and N_β is a single bond, or a double bond whereby
 25 R2 (and H on C_α) are nil;

- (b) the bond between C₅ and C₆ is a single bond, or a double bond whereby R₁₃ and R₁₅ are nil; the bond between C₆ and C₇ is a single bond, or a doublebond whereby R₁₁ and R₁₃ are nil; but the C₅-C₆ and C₆-C₇ bonds are not both double bonds;
- 5 (c) R₁ is selected from alkyl, aryl, and heterocycle;
- (d) R₂, if not nil, is selected from hydrogen, alkyl, alkylacyl, arylacyl, alkylsulfonyl and arylsulfonyl;
- (e) R₃, R₄ and R₅ are each independently selected from hydrogen, halo, alkyl, aryl, heterocycle, nitro, cyano, and unsubstituted or alkyl- or aryl- or heterocycle-substituted hydroxy, thio, amino, amide, formyl (acyl), carboxy, and carboxamide; or R₃ and R₄ together are alkylene or heteroalkylene attached to adjacent carbons of the phenyl to which R₃ and R₄ are attached, and R₅ is as specified in (e) above;
- 10
- (f) R₆, R₇ and R₈ are each independently selected from the group consisting of hydrogen, halo, alkyl, aryl, heterocycle, nitro, cyano, and unsubstituted or alkyl- or aryl- or heterocycle-substituted hydroxy, thio, amino, amide, sulfonamide, formyl (acyl), carboxy, and carboxamide; or R₆ and R₇ together are alkylene or heteroalkylene attached to adjacent carbons of the phenyl to which R₆ and R₇ are attached, and R₈ is as specified in (f) above;
- 15
- (g) R₉ is selected from hydrogen, halo, alkyl, aryl, heterocycle, and carboxy and its alkyl and aryl esters and amides;
- 20
- (h) R₁₀, R₁₂ and R₁₄, and R₁₁, R₁₃ and R₁₅, if not nil, are each independently selected from hydrogen, alkyl, and aryl;

and an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof.

25

The subject invention also includes compositions comprising a subject compound and a pharmaceutically-acceptable excipient; and methods for treating or preventing diseases or disorders by administering to a human or lower animal in need thereof, a safe and effective amount of a subject compound.

DETAILED DESCRIPTION OF THE INVENTION

As used herein unless specified otherwise, "alkyl" means a hydrocarbon chain which is branched, linear or cyclic, saturated or unsaturated (but not aromatic), substituted or unsubstituted. The term "alkyl" may be used alone or as part of another word where it may be shortened to "alk" (e.g., in alkoxy, alkylacyl). Preferred linear alkyl have from one to about twenty carbon atoms, more preferably from one to about ten carbon atoms, more preferably still from one to about six carbon atoms, still more preferably from one to about four carbon atoms; most preferred are methyl or ethyl. Preferred cyclic and branched alkyl have from three to about twenty carbon atoms, more preferably from three to about ten carbon atoms, more preferably still from three to about seven carbon atoms, still more preferably from three to about five carbon atoms. Preferred cyclic alkyl have one hydrocarbon ring, but may have two, three, or more, fused hydrocarbon rings. Preferred alkyl are unsaturated with from one to about three double or triple bonds, preferably double bonds; more preferably they are mono-unsaturated with one double bond. Still more preferred alkyl are saturated. Saturated alkyl are referred to herein as "alkanyl". Alkyl unsaturated only with one or more double bonds (no triple bonds) are referred to herein as "alkenyl". Preferred substituents of alkyl include halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides, nitro, and cyano. Also, unsubstituted alkyl are preferred.

As used herein, "heteroatom" means a nitrogen, oxygen, or sulfur atom.

As used herein, "alkylene" means an alkyl which connects two other moieties, "heteroalkylene" means an alkylene having one or more heteroatoms in the connecting chain.

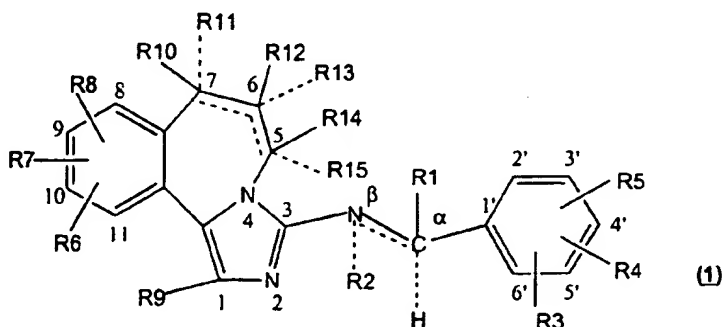
As used herein unless specified otherwise, "aryl" means an aromatic hydrocarbon ring (or fused rings) which is substituted or unsubstituted. The term "aryl" may be used alone or as part of another word (e.g., in aryloxy, arylacyl). Preferred aryl have from six to about fourteen, preferably to about ten, carbon atoms in the aromatic ring(s), and a total of from about six to about twenty, preferably to about twelve, carbon atoms. Preferred aryl is phenyl or naphthyl; most preferred is phenyl. Preferred substituents of aryl include halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino,

alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides, nitro, and cyano. Also, unsubstituted aryl are preferred.

As used herein unless specified otherwise, "heterocycle" means a saturated, unsaturated or aromatic cyclic hydrocarbon ring (or fused rings) with one or more heteroatoms in the hydrocarbon ring(s). Preferred heterocycles have from one to about six heteroatoms in the ring(s), more preferably one or two or three heteroatoms in the ring(s). Preferred heterocycles have from three to about fourteen, preferably to about ten, carbon plus heteroatoms in the ring(s), more preferably from three to about seven, more preferably still five or six, carbon plus heteroatoms in the rings(s); and a total of from three to about twenty carbon plus heteroatoms, more preferably from three to about ten, more preferably still five or six, carbon plus heteroatoms. Preferred heterocycles have one ring, but may have two, three, or more, fused rings. More preferred heterocycle rings include those which are one ring with 5 or 6 carbon plus heteroatoms in the ring with no more than three ring heteroatoms, no more than two of which are O and S. Still more preferred are such 5- or 6-ring atom heterocycles with one or two ring atoms being O or S and the others being C; or with one, two or three ring atoms being N and the others being C. Such preferred 5- or 6-ring atom heterocycles are preferably saturated, unsaturated with one or two double bonds, or aromatic. Such preferred 5- or 6-ring atom heterocycles are preferably a single ring; or fused with a 3- to 6-ring atom hydrocarbon ring which is saturated, unsaturated with one double bond, or aromatic (phenyl); or fused with another such 5- or 6-ring atom heterocyclic ring. Heterocycles are unsubstituted or substituted. Preferred heterocycle substituents are the same as for alkyl.

Compounds of the Invention

The subject invention involves compounds having the following structure:



In structure 1, the bond between the α carbon and the β nitrogen can be either a single bond, in which case R2 and the H attached to the α carbon exist, or a double bond, in which case R2 and that H do not exist (are nil). This C_{α} - N_{β} bond is preferably a single bond.

5 In structure 1, the bonds between carbons 5 and 6 and between carbons 6 and 7 can both be single bonds or one can be a double bond. If the C_5 - C_6 bond is a double bond, R13 and R15 do not exist (are nil). If the C_6 - C_7 bond is a double bond, R11 and R13 do not exist (are nil). Preferably, the C_5 - C_6 and C_6 - C_7 bonds are both single bonds.

In structure 1, R1 is selected from hydrogen, alkyl, aryl, and heterocycle. Preferred
10 R1 include linear alkanyl having from 1 to about 6 carbon atoms, linear alkenyl having from 2 to about 6 carbon atoms, and branched and cyclic alkanyl and alkenyl having from 3 to about 6 carbon atoms, such alkenyl preferably having 1 double bond. Such preferred alkanyl and alkenyl are preferably unsubstituted, or substituted with phenyl, heterocycle having 5 or 6 ring atoms, carboxy and its C_1 - C_6 alkyl and phenyl esters, or cyano. More
15 preferably such alkanyl and alkenyl have up to about 7 carbon atoms, more preferably still up to 6 carbon atoms, still more preferably up to 4 carbon atoms. Most preferred R1 is unsubstituted methyl. Also preferred is R1 being hydrogen.

In structure 1, R2, if it exists, is selected from hydrogen, alkyl, alkylacyl, arylacyl, alkylsulfonyl, and arylsulfonyl. Preferred R2 is selected from hydrogen; C_1 - C_6 alkyl, such
20 alkyl being saturated or unsaturated with one double bond and unsubstituted or substituted with phenyl; C_1 - C_6 alkylacyl, the alkyl being saturated or unsaturated with one double bond; and phenylacyl. More preferred is the alkyl portions of the aforementioned moieties being C_1 - C_4 and saturated. More preferred still is R2 being methyl. Most preferred R2 is hydrogen.

25 In structure 1, R3, R4 and R5 are each independently selected from hydrogen, halo, alkyl, aryl, heterocycle, nitro and cyano; also from hydroxy, thio, amino, amide, formyl (acyl), carboxy, and carboxamide which are unsubstituted or substituted, preferably with alkyl or aryl or heterocycle; or R3 and R4 together are alkylene or heteroalkylene attached to adjacent carbon atoms of the phenyl ring, thereby forming a cycloalkyl or aryl or
30 heterocycle ring which is fused to the phenyl ring (phenyl of carbons 1'-6'), and R5 is as defined above. Preferred R3, R4 and R5 are selected from hydrogen, halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino,

arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl or aryl esters and amides; more preferably from hydrogen, halo, alkyl, alkoxy, phenoxy, thio, alkylthio, phenylthio, mono- or dialkylamino, mono- or diphenylamino, alkylacyl, and phenylacyl. Alkyl portions of such substituents are preferably about C1-C6, more preferably about C1-C4, more preferably still methyl or ethyl. Alkyl and phenyl R3, R4 or R5 substituents or portions of such substituents are preferably unsubstituted or substituted with from 1 to about 3 fluoro, more preferably unsubstituted. More preferred is for from one to three of R3, R4, and R5 being halo, the other(s) being hydrogen. Also more preferred is for from one to three of R3, R4 and R5 being methyl or ethyl, the other(s) being hydrogen. Also preferred is R3 being dialkylamino, the alkyls having from 1 to about 6 carbon atoms, preferably from about 1 to about 4 carbon atoms, and R4 and R5 being hydrogen, R3 preferably being attached to the 4' carbon. More preferred still is for from one to three of R3, R4 and R5 being independently selected from F, Cl and Br, the other(s) being hydrogen; still more preferred, when two or three of R3, R4 and R5 are F, Cl or Br, they are the same. Also more preferred is from one to three of R3, R4 and R5 being unsubstituted methyl, the other(s) being hydrogen. Also more preferred is one or two of R3, R4 and R5 being trifluoromethyl, the other(s) being hydrogen or halo, and if halo, preferably fluoro. Also more preferred is one or two of R3, R4 and R5 being methoxy or trifluoromethoxy, the others being hydrogen or halo, and if halo, preferably fluoro.

Also preferred are R3 and R4, which are attached to adjacent carbon atoms of the phenyl ring, together being a saturated or unsaturated alkylene or heteroalkylene having from 1 to about 6 carbon atoms and from 0 to about 3 heteroatoms, thus forming a ring fused to the phenyl, such ring having from about 5 to about 8 ring atoms. Such ring fused to the phenyl preferably has from about 5 to about 6 ring atoms of which from 0 to 2, more preferably 0 or 1, are heteroatoms. Preferred fused rings (including the phenyl to which R3 and R4 are attached) include naphthyl, indolyl, benzimidazolyl, benzofuryl, benzopyranyl. When R3 and R4 form a ring fused with the phenyl, R5 is preferably H.

In structure 1, R6, R7 and R8 are each independently selected from hydrogen, halo, alkyl, aryl, heterocycle, cyano and nitro; also from hydroxy, thio, amino, amide, formyl (acyl), carboxy, carboxamide, and sulfonamide which are unsubstituted or substituted, preferably with alkyl or aryl or heterocycle; or R3 and R4 together are alkylene or heteroalkylene attached to adjacent carbon atoms of the phenyl ring, thereby forming a

cycloalkyl or aryl or heterocycle ring which is fused to the phenyl ring (phenyl of carbons 7-10), and R5 is as defined above. Preferred R6, R7 and R8 are selected from hydrogen, halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, sulfonamide, alkylsulfonamide, arylsulfonamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides; more preferably from hydrogen, halo, hydroxy, C₁-C₄ alkoxy, thio, C₁-C₄ alkylthio, C₁-C₄ alkyl esters and amides of carboxy, and heterocycle having 5 or 6 ring atoms. More preferably one or two of R6, R7 and R8 are selected such that at least one heteroatom is bonded directly to the phenyl ring. When two heteroatoms are bonded directly to different carbons, preferably adjacent carbons, of the phenyl ring, those heteroatoms may be connected by an alkylene moiety, the alkylene moiety preferably having from 1 to about 4, more preferably 1 or 2, carbon atoms. Preferred is for one or two of R6, R7 and R8 being non-hydrogen moieties bonded to the fused rings at carbons 8 and/or 9 (as in structure 2 below); more preferred is that two of them be non-hydrogen moieties bonded to carbons 8 and 9. More preferred still is that R8 is hydrogen and that R6 and R7 are both alkoxy or both alkylthio bonded to carbons 8 and 9, respectively; preferably both R6 and R7 are the same. Preferred alkyl portions of R6 and R7 have from 1 to about 4 carbon atoms, more preferably 1 or 2 carbon atoms; most preferred is methyl. Such alkyl portions are preferably unsubstituted. Such alkyl portions are preferably saturated. Most preferred is that both R6 and R7 are methoxy bonded to carbons 8 and 9, R8 being hydrogen.

Also preferred are R6 and R7, which are attached to adjacent carbon atoms of the phenyl ring, together being a saturated or unsaturated alkylene or heteroalkylene having from 1 to about 6 carbon atoms and from 0 to about 3 heteroatoms, thus forming a ring fused to the phenyl, such ring having from about 5 to about 8 ring atoms. Such ring fused to the phenyl preferably has from about 5 to about 6 ring atoms of which from 0 to 2, more preferably 0 or 1, are heteroatoms. Preferred rings formed by R6 and R7 include phenyl, furyl, pyrrolyl, dioxanyl, imidazolyl, pyridinyl, pyrrolidinyl, piperidinyl. When R6 and R7 form a fused ring, R8 is preferably H.

In structure 1, R9 is selected from hydrogen, halo, alkyl, aryl, heterocycle, carboxy and its alkyl esters and amides. Preferred R9 is selected from hydrogen, halo, C₁-C₄ alkyl, phenyl. More preferred R9 is selected from hydrogen and unsubstituted and substituted

phenyl; substituents on such phenyl are preferably selected from hydroxy, alkoxy, thio and alkylthio. Most preferred R9 is hydrogen.

In structure 1, R10, R12 and R14, and R11, R13 and R15 if they exist, are each independently selected from hydrogen, alkyl and aryl. Preferred R10, R12 and R14, and
5 R11, R13 and R15 if they exist, are selected from hydrogen and alkyl having from 1 to about 4 carbon atoms, especially unsubstituted methyl or ethyl. Most preferred is for R10, R12 and R14, and R11, R13 and R15 if they exist, to all be hydrogen.

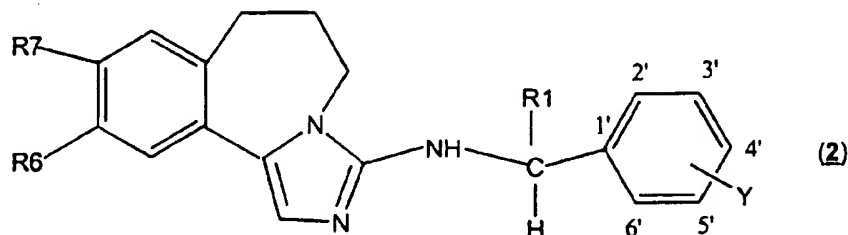
The subject invention includes optical isomers, diastereomers, and enantiomers of the compounds of structure 1. The subject invention includes pharmaceutically-acceptable
10 salts, hydrates, and biohydrolizable esters, amides and imides of such compounds.

A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic group (e.g., carboxy group), or an anionic salt formed at any basic group (e.g., amino group) on a compound of structure 1. Many pharmaceutically-acceptable salts are known. Preferred
15 cationic salts include the alkali metal salts, such as sodium and potassium, alkaline earth metal salts, such as magnesium and calcium, and organic salts, such as ammonium. Preferred anionic salts include halides, sulfonates, carboxolates, phosphates, and the like. Salts of addition may provide an optical center where once there was none.

The compounds of the subject invention, and salts thereof, may have one or more chiral centers. The invention includes all optical isomers of the compounds of structure 1
20 and salts thereof, including diastereomers and enantiomers. The subject invention includes and contemplates each optical isomer, diastereomer or enantiomer thereof, in purified form, substantially purified form, and mixtures, including racemic mixtures.

For compounds of structure 1 having a single C_α-N_β bond and different R1 and R2 moieties, the α carbon is stereogenic. For such compounds, those having the R stereoscopic
25 configuration are generally preferred over those having the S configuration.

Preferred compounds of the subject invention include those having structure 2:



in structure 2, R1, R6, and R7 are as described hereinabove, and Y is the combinations of R3, R4 and R5 described hereinabove.

In structure 2, R1 is preferably selected from linear alkanyl having from one to four carbon atoms; linear alkenyl having one double bond and from two to four carbon atoms, 5 branched and cyclic alkanyl having from three to five carbon atoms, and branched and cyclic alkenyl having one double bond and from three to five carbon atoms. Such preferred R1 are unsubstituted or substituted with one phenyl, more preferably are unsubstituted. More preferred R1 is selected from methyl, ethyl, ethenyl, n-propyl, i-propyl, n-propenyl, i-propenyl, s-butyl, cyclopropyl, cyclobutyl, and cyclopentyl. More preferred still R1 is 10 selected from methyl, ethyl, ethenyl, i-propyl, and n-propenyl. Most preferred R1 is methyl.

In structure 2, one or both of R6 and R7, preferably both, are preferably alkylthio or more preferably alkoxy with alkanyl having from one to four carbon atoms. If one of R6 and R7 is not alkylthio or alkoxy, it is preferably hydrogen. More preferred is both R6 and 15 R7 being methoxy or ethoxy; most preferred is both R6 and R7 being methoxy.

In structure 2, Y is preferably selected from all hydrogen; mono-, di-, or trihalo, preferably selected from fluoro, chloro and bromo, preferably in one or more of the 2', 3', 4' and 5' positions; mono- di-, and trimethyl, preferably in one or more of the 2', 3', 4' and 6' positions; and mono- or di-trifluoromethyl, preferably in one or both of the 3' and 5' 20 positions. Also preferred is Y being diakylamino, preferably in the 4' position, the two alkyls preferably being the same and preferably having from 1 to 4 carbon atoms. More preferred Y is selected from 4'-fluoro, 4'-chloro, 4'-bromo, 2',4'-difluoro, 2',4'-dichloro, 2',4'-dibromo, 2',4',5'-trifluoro, 2',4',5'-trichloro, 3',4'-difluoro, 3',4'-dichloro, 3',4'-dibromo, 4'-methyl, 2',4'-dimethyl, 2',4',6'-trimethyl, 3'-trifluoromethyl, 3',5'-di- 25 trifluoromethyl, and 4'-dibutylamino. Also preferred Y is selected from 2',4'-dihalo and 3',4'-dihalo, where one halo is selected from fluoro, chloro, and bromo, and the other halo is a different one of those three; more preferably one of such halo is fluoro. Most preferred Y is selected from 4'-chloro, 4'-bromo, and 2',4'-dichloro.

Non-limiting examples of compounds of the subject invention include those of 30 structure 2 wherein R6 and R7 are both methoxy, and R1 and Y are as indicated in the following table:

Example

R1

Y

1	methyl	hydrogen
2	methyl	4'-fluoro
3	methyl	4'-chloro
4	methyl	4'-bromo
5	methyl	2',4'-difluoro
6	methyl	2',4'-dichloro
7	methyl	2'-fluoro, 4'-chloro
8	methyl	2'-fluoro, 4'-bromo
9	methyl	2'-chloro, 4'-fluoro
10	methyl	2'-bromo, 4'-fluoro
11	methyl	3',4'-difluoro
12	methyl	3',4'-dichloro

<u>Example</u>	<u>R1</u>	<u>Y</u>
13	methyl	3'-fluoro, 4'-chloro
14	methyl	3'-fluoro, 4'-bromo
15	methyl	3'-chloro, 4'-fluoro
16	methyl	3'-bromo, 4'-fluoro
17	methyl	2',4',5'-trifluoro
18	methyl	4'-methyl
19	methyl	2',4'-dimethyl
20	methyl	3',4'-dimethyl
21	methyl	2',4',6'-trimethyl
22	methyl	3'-trifluoromethyl
23	methyl	3',5'-di-trifluoromethyl
24	methyl	4'-fluoro, 3'-trifluoromethyl
25	ethyl	4'-fluoro
26	ethyl	4'-chloro
27	ethyl	4'-bromo
28	ethyl	2',4'-dichloro
29	ethyl	3'-fluoro, 4'-chloro
30	ethenyl	4'-chloro
31	ethenyl	2',4'-dichloro
32	i-propyl	4'-fluoro
33	i-propyl	4'-chloro
34	i-propyl	4'-bromo
35	i-propyl	2',4'-dichloro
36	i-propyl	3'-fluoro, 4'-chloro
37	-CH ₂ -CH=CH ₂	4'-fluoro
38	-CH ₂ -CH=CH ₂	4'-chloro
39	-CH ₂ -CH=CH ₂	2',4'-dichloro
40	s-butyl	4'-chloro
41	cyclopentyl	4'-chloro
42	methyl	2',4',5'-trifluoro

43

methyl

2',3',4'-trifluoro



<u>Example</u>	<u>R1</u>	<u>Y</u>
44	ethyl	2',4',5'-trifluoro
45	ethyl	2',3',4'-trifluoro
46	i-propyl	2',4',5'-trifluoro
47	i-propyl	2',3',4'-trifluoro
48	methyl	4'-dibutylamino
49	ethyl	4'-dimethylamino
50	i-propyl	4'-diethylamino
51	cyclohexyl	4'-fluoro
52	s-butyl	4'-fluoro
53	methyl	3'-methyl
54	s-butyl	all hydrogen
55	s-butyl	n-propoxy
56	s-butyl	2',3'-dimethoxy
57	s-butyl	4'-phenoxy
58	s-butyl	3'-trifluoromethoxy
59	s-butyl	3'-methoxy, 4'-hydroxy
60	s-butyl	2'-fluoro
61	n-hexyl	3-(dimethylamino)propoxy
62	n-hexyl	4'-i-propyl
63	n-hexyl	4'-t-butoxy
64	n-hexyl	1',5'-dimethyl-4'-methoxy
65	n-hexyl	4'-trifluoromethyl
66	n-hexyl	2'-methyl
67	n-hexyl	3',4'-dichloro
68	s-butyl	1'-naphthyl
69	s-butyl	4'-dimethylamino-1'- naphthyl

In addition, it is recognized that for purification, administration, and the like, the salts and other derivatives of the above compounds can be used. Thus a pharmaceutically-

acceptable salt, hydrate, or biohydrolizable ester, amide or imide thereof is contemplated as part of the subject invention.

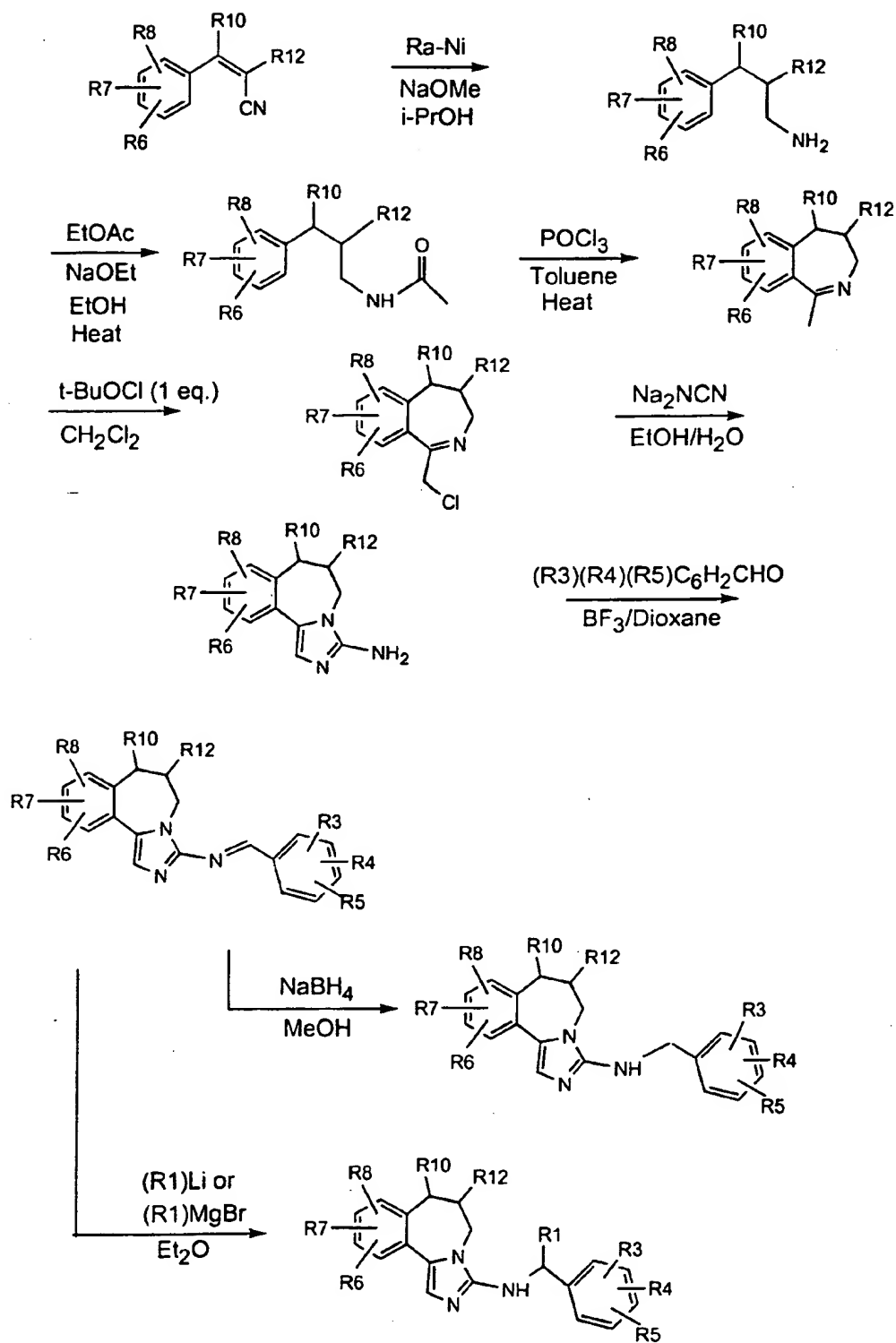
Methods of Making the Compounds

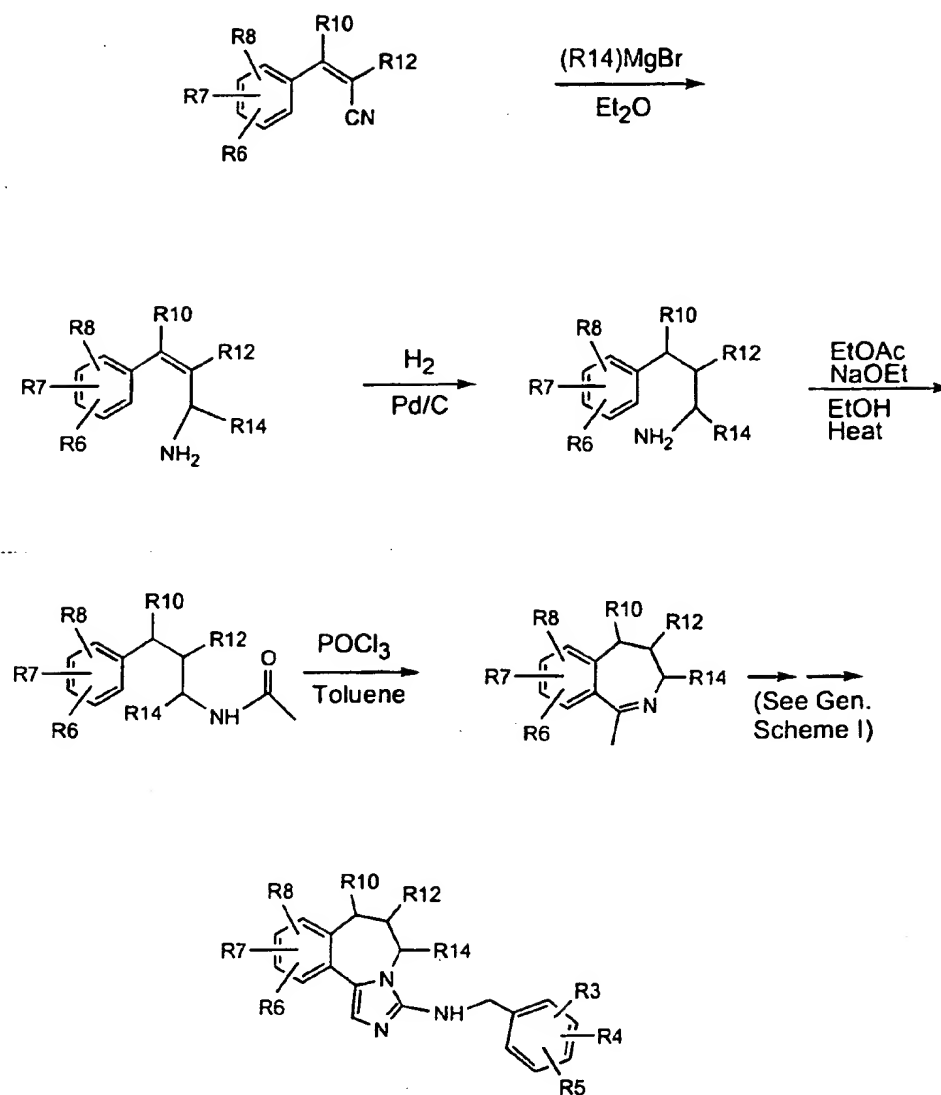
In making the compounds of the subject invention, the order of synthetic steps may
5 be varied to increase yield of desired product. The skilled artisan will recognize that the judicious choice of reactants, solvents, and temperatures is important in successful synthesis. The starting materials used in preparing the subject compounds are known, made by known methods, or are commercially available.

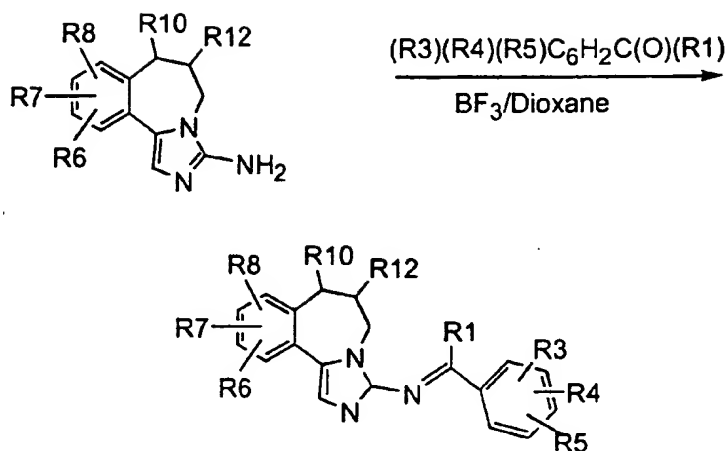
It is recognized that the skilled artisan can readily carry out standard manipulations
10 of organic compounds without further direction. These include, but are not limited to, reduction, oxidation, acylation, substitution, etherification, esterification, sulfonation, and the like. Examples of these manipulations are discussed in standard texts.

Procedures for preparing some imidazo-isoquinoline compounds are disclosed in
U.S. Patent No. 3,917,610 issued November 4, 1975, and U.S. Patent No. 4,143,143 issued
15 on March 6, 1979, both of which are incorporated herein by reference.

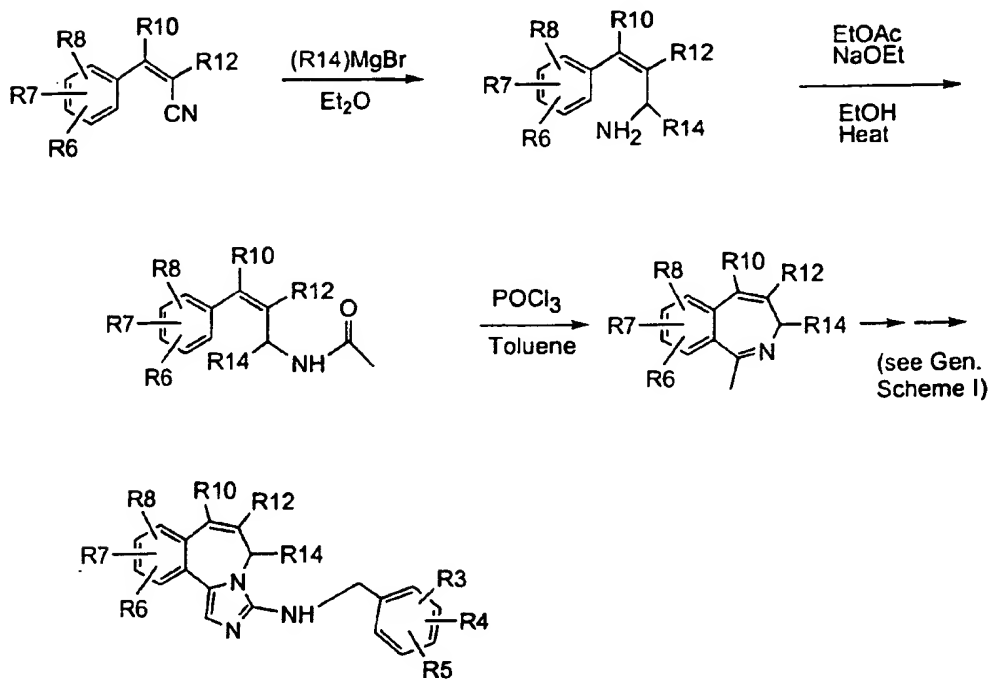
The following general schemes can be used for synthesizing compounds of the subject invention.

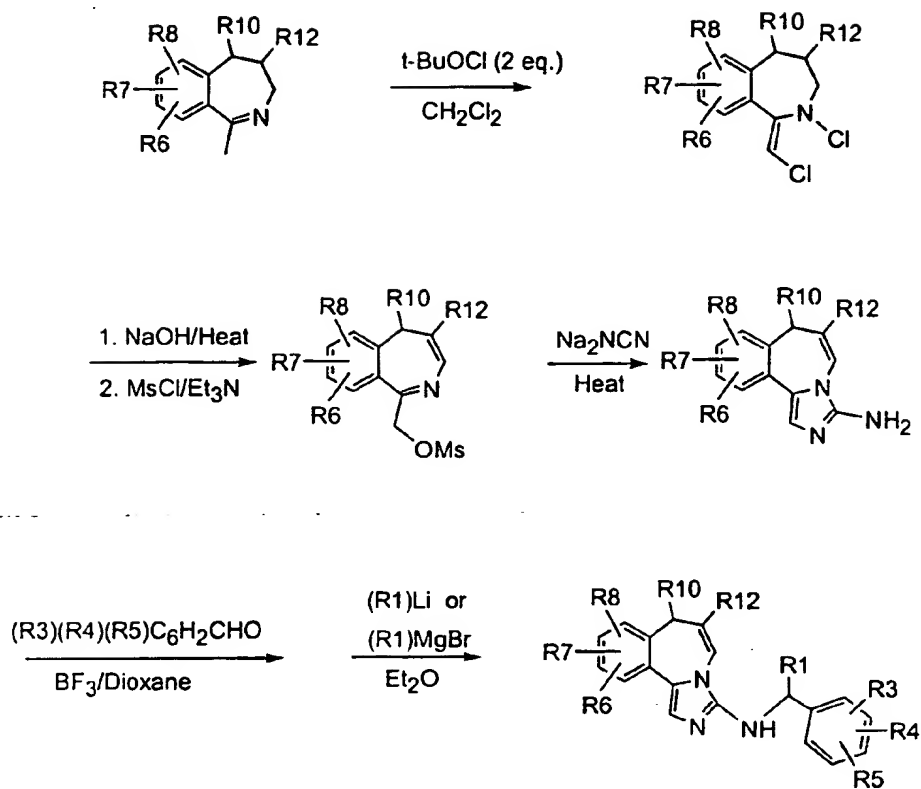
General Scheme I

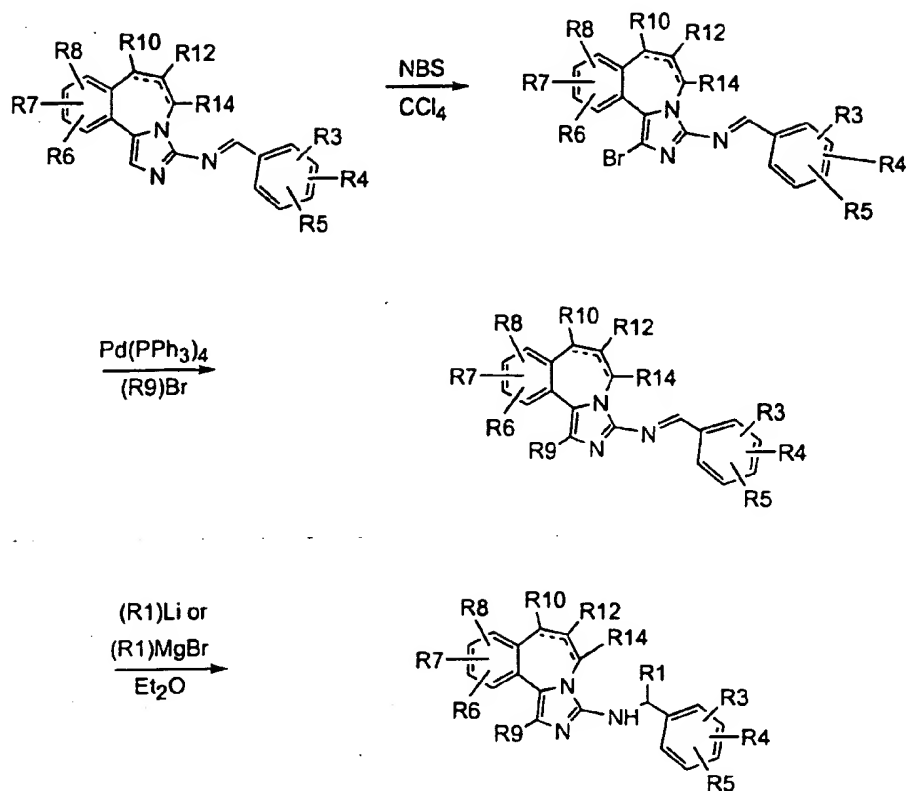
General Scheme II

General Scheme III

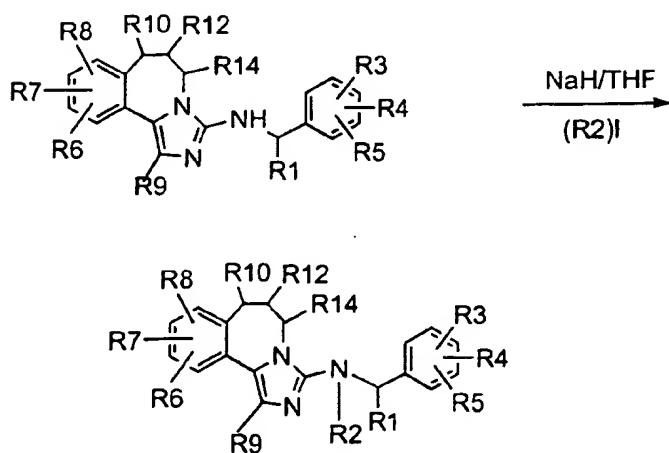
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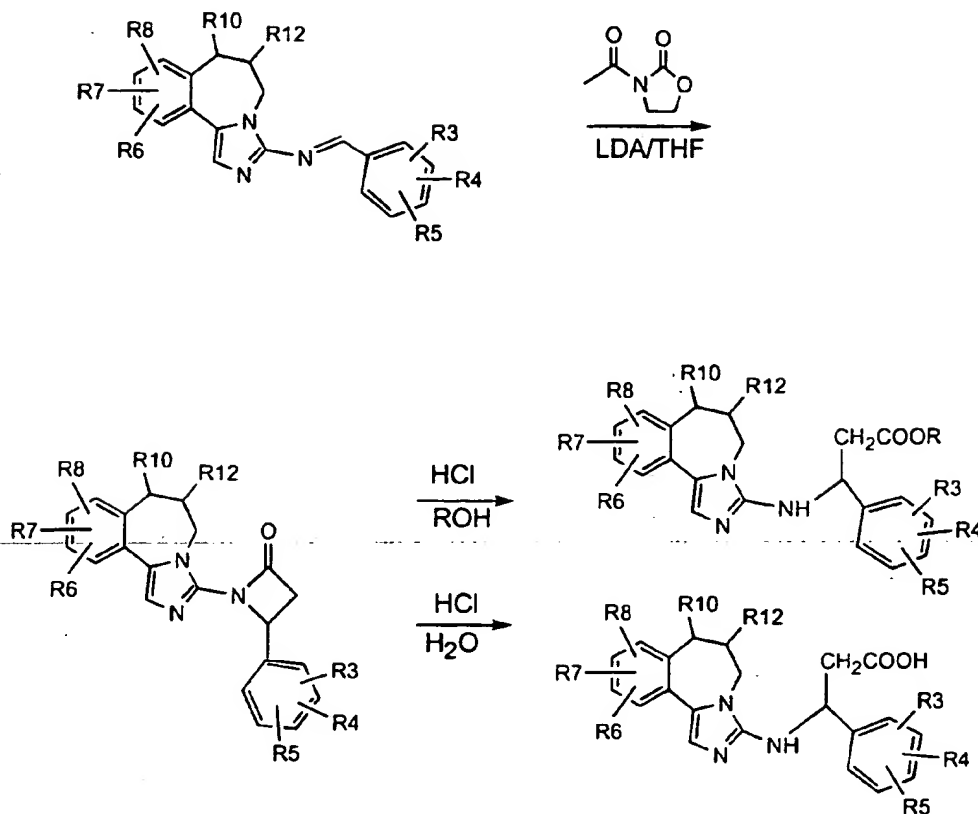
General Scheme IV

General Scheme V

General Scheme VI

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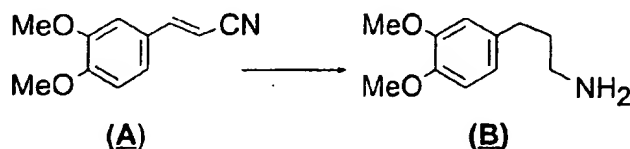
General Scheme VII

General Scheme VIII

- 5 The following examples provide further information regarding synthesis of the subject invention compounds:

Example B

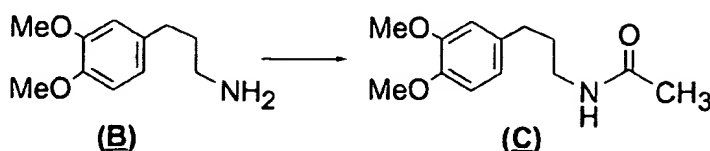
10



- 15 **Preparation of amine B.** Preparation of Raney-Ni: a large excess of Raney-Ni is washed with H₂O three times and i-PrOH twice to be ready for use. In a hydrogenation bottle, compound A (Aldrich Chem. Co. Milwaukee, WI) (4.0 g, 20 mmol) in iPrOH (50 mL) is mixed with NaOMe (1.14 g, 20 mmol). A large excess amount of Raney-Ni in iPrOH is subsequently added. The bottle is placed onto a hydrogenation apparatus under H₂ (40 psi) and shaken for 24 h. The reaction is checked by TLC. After the reaction is

complete, this mixture is filtered under N₂ (caution: Ni will catch fire in the air). Concentration of the filtrate provides compound **B** as a yellow residue.

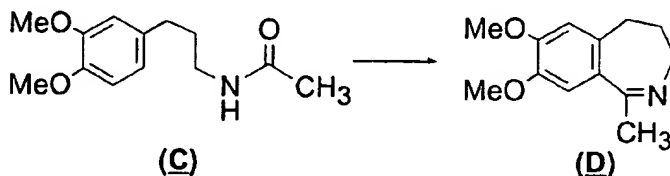
Example C



Preparation of the amide C. To a NaOEt solution (50 mL) prepared by adding Na (295 mg, 12.8 mmol) to absolute ethanol, **B** is added (2.52 g, 12.8 mmol) in ethanol (5 mL). The mixture is stirred for 10 min. Ethyl acetate (10 mL) is added into the solution. The mixture is then refluxed under N₂ for 6 h. After the reaction is completed, the solvent is evaporated and compound **C** is crystallized from EtOH.

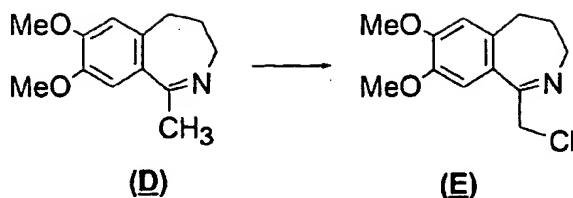
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Example D

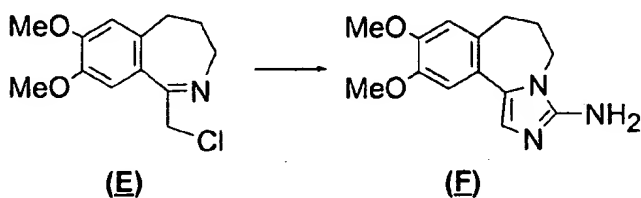


POCl₃ catalyzed cyclization. A solution of **C** (2.4 g, 10 mmol) in 30 mL toluene is added slowly (for a period of 20 h, using a syringe pump) to a refluxing POCl₃/toluene solution (1:3, 70 mL total in volume) under nitrogen. After the addition, the reaction is refluxed for another 5 h and monitored by TLC. Concentration of the solvent under vacuum gives a residue. This crude mixture is partitioned with CH₂Cl₂ and H₂O. The aqueous layer is neutralized with NH₃·H₂O and extracted with CH₂Cl₂. The combined organic extracts are washed with brine and dried over Na₂SO₄. Removal of the solvent gives crude product. Purification using Al₂O₃ chromatography (eluant ethyl acetate/hexane in gradient from 1:1 to 4:1) affords compound **D**.

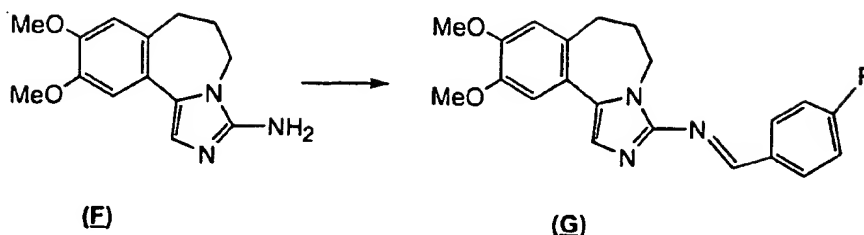
20

Example E

Chloronation of the imine. Compound **D** (260 mg, 1.22 mmol) is dissolved in CH₂Cl₂ (10 mL) at -5 °C (ice and acetone bath), under N₂. To this solution is added dropwise tert-butylhypochlorite (120 mg, 120 μL). TLC is used to follow the reaction closely (begin to check after 0.5 h). When the reaction is complete, removal of solvent affords compound **E**.

Example F

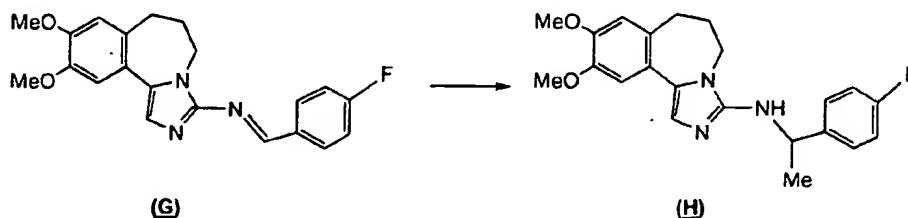
9,10-Dimethoxy-6,7-dihydro-5H-imidazo[5,1-a]benzazepin-3-amine **F.** A solution of Na₂NCN (180 mg, 2.1 mmol) in 1.5 mL of H₂O and 15 mL of EtOH under N₂ is heated to reflux. Solid compound **E** (200 mg, 0.8 mmol) is added portionwise to the solution. The mixture is stirred at reflux for 2 h. Two TLC (CH₂Cl₂/MeOH 8.5:1.5 and 9.5:0.3) are used to check for the reaction product and remaining starting material, respectively. After the reaction is complete, concentration of the solution gives a semisolid residue. 2 mL H₂O (volume should be controlled to minimum) is added and insoluble compound **F** is removed by filtration. The filtrate is extracted with CH₂Cl₂ twice. The extracts are washed with 5% aqueous NaHCO₃ once, and are dried over Na₂SO₄. Evaporation of the solvent gives crude compound **F**. Purification by column chromatography (eluant CH₂Cl₂:MeOH:NH₄OH in gradient from 500:10:0 to 500:40:1) gives compound **F**.

Example GFormation of Benzylidene G.

5 Method 1: A mixture of **F** (3 mmol) and substituted benzaldehyde 4-F-C₆H₄CHO (10 mmol) in 35 mL of absolute EtOH is refluxed for 14 h. If the Y-benzaldehyde is not reactive enough, molecular sieves are added to drive the reaction by removing H₂O. Evaporation of the solvent and chromatography of the resultant residue provides imine **G**. This method 1 works well when substituents on the benzene ring are H, or electron
10 withdrawing groups.

Method 2: To a solution of the compound **F** (1mmol) and 4-F-benzaldehyde (3 mmol) in 10 mL of anhydrous 1,4-dioxane, BF₃-Et₂O (3 drops) is added and the mixture is heated to 80 °C under N₂ for 2 h. More BF₃-Et₂O is sometimes needed to drive the reaction to
15 completion. The solvent is evaporated thoroughly to give a crude residue which is partitioned in CH₂Cl₂ and 5% aqueous NaHCO₃ (2:1). The separated aqueous layer is extracted with CH₂Cl₂. The combined organic extracts are washed with brine and dried over Na₂SO₄. Purification of crude product by chromatography gives imine **G**. This method 2 can be used with most substituted benzaldehydes.

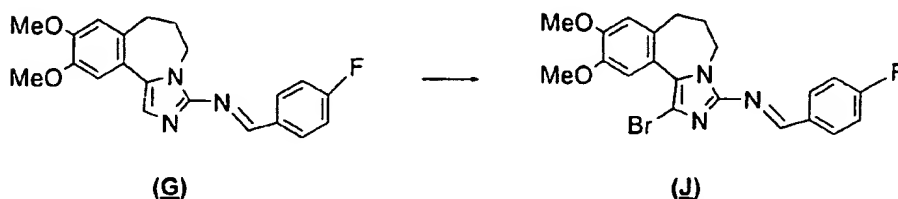
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Example H

25 N-(4-F-phenylmethyl)-9,10-dimethoxy-6,7-dihydro-5H-imidazo[5,1-a][2]-benzazepin-3-amine H. MeMgBr (2.8M concentration, 1.2 mmol) in Et₂O is added dropwise to a solution of **G** (1 mmol) in 10 mL of anhydrous THF at 0 °C under N₂. The mixture is stirred at room temperature for 15 min. TLC (CH₂Cl₂/MeOH 9:1) is used to monitor the reaction. After completion, ethyl acetate and then MeOH are added to

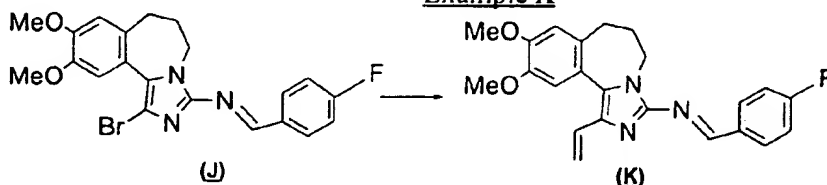
destroy excess Grignard reagent. Concentration of the solution gives a white solid residue. It is partitioned in CH_2Cl_2 /5% aqueous NaHCO_3 (1:1). The aqueous layer is extracted with CH_2Cl_2 . The extracts are washed with 5% aqueous NaHCO_3 and brine, and are dried over Na_2SO_4 . The crude residue after evaporation is purified by chromatography to provide compound **H**.

Example J



N-(4-F-benzylidene)-1-bromo-9,10-dimethoxy-6,7-dihydro-5H-imidazo[5,1-a][2]-benzazepin-3-amine J. N-Bromosuccinimide (NBS) solid (98 mg, 0.55 mmol) is added to a solution of compound **G** (0.5 mmol) in 15 mL of CCl_4 . Radical initiator benzoyl peroxide (2 mol%) is subsequently added. The flask is placed in a 90 °C oil bath. After 10 min stirring, TLC (CHCl_3 /MeOH 9:0.3) indicates the reaction is complete. Filtration of the mixture through a celite pad and evaporation of the filtrate give a residue. Purification of the crude residue by chromatography affords compound **J**.

Example K

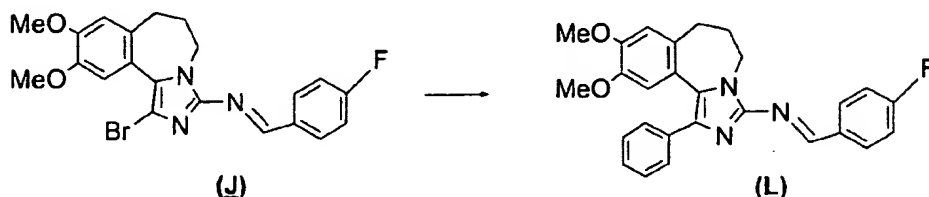


Stille coupling to form K. To a solution of **J** (0.22mmol) and $\text{Pd}(\text{PPh}_3)_4$ (13mg, 0.056mmol) in 7 mL of anhydrous toluene are added vinyltributyltin (0.072 mL, 0.26mmol) and a few crystals of 2,6-di-tert-butyl-4-methylphenol. The reaction mixture is allowed to reflux at 110 °C under a nitrogen atmosphere. Total reflux time is 6 hours. Thin-layer chromatography (TLC) using a 9.9:0.1 CH_2Cl_2 /MeOH eluant system indicates completion of the reaction. The reaction mixture is allowed to cool, and is then diluted with 1-2 mL of ethyl acetate (EtOAc). The resultant mixture is washed with water, brine, extracted with EtOAc, dried over Na_2SO_4 , and filtered. The filtrate is treated with 3 mL of 30% aqueous KF at room temperature for 2h. The light purple-violet solid is filtered off. The filtrate is diluted with EtOAc and washed with water, 30% aqueous NH_4OH (3X), and brine, then extracted with EtOAc, dried (Na_2SO_4), and concentrated *in vacuo*.

to yield crude product. Chromatography (silica gel) with a gradient elution system of CH_2Cl_2 and 9.7:0.3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ gives compound K.

Example L

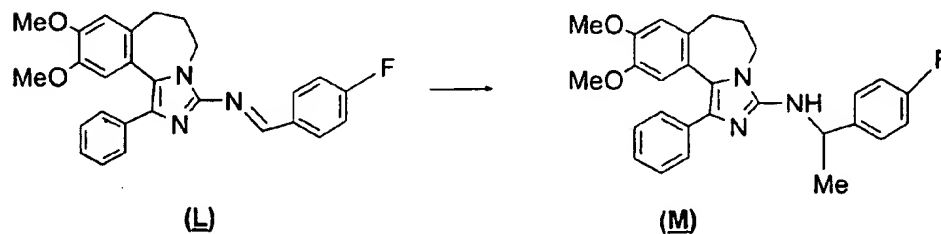
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Suzuki coupling to form L. To a solution of J (1.1 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (76 mg, 0.066 mmol) in 25 mL of distilled xylene is added 1.1 mL of 2M Na_2CO_3 . The reaction mixture is placed under a nitrogen atmosphere. Heat is added to the system to completely dissolve the starting material. A boronic acid solution is prepared by adding benzeneboronic acid (2.2 mmol) to 2 mL of hot absolute ethanol. The boronic acid solution is added dropwise to the refluxing reaction mixture over 2 h. The reaction mixture is allowed to reflux for 21 hours, and is then cooled. The catalyst is removed by filtration through a celite pad. The filtrate is concentrated on a vacuum rotavapor apparatus. The residual is partitioned in 1:1 $\text{CH}_2\text{Cl}_2/\text{brine}$, extracted with CH_2Cl_2 , dried over Na_2SO_4 , and filtered over a bed of Na_2SO_4 . The filtrate is concentrated *in vacuo* to yield crude product. Chromatography (silica gel) with 2.5:7.5 ethyl acetate/hexane produces L as an orange solid.

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Example M

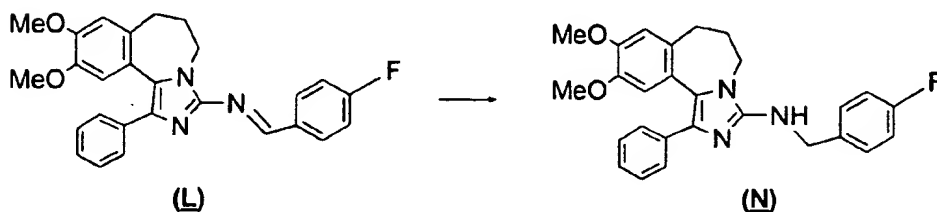


N-(4-F-phenylmethyl)-1-phenyl-9,10-dimethoxy-6,7-dihydro-5H-imidazo[5,1-a][2]-benzazepin-3-amine M. MeMgBr (2.8M concentration, 1.2 mmol) in Et_2O is added dropwise to a solution of L (1 mmol) in 10 mL of anhydrous THF at 0 °C under N_2 . The mixture is stirred at room temperature for 15 min. TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) is used to monitor the reaction. After completion, ethyl acetate and then MeOH are added to destroy excess Grignard reagent. Concentration of the solution gives a white solid residue

which is partitioned in CH₂Cl₂/5% aqueous NaHCO₃ (1:1). The aqueous layer is extracted with CH₂Cl₂. The extracts are washed with 5% aqueous NaHCO₃ and brine, and dried over Na₂SO₄. The crude residue after evaporation is purified by chromatography to provide compound M.

5

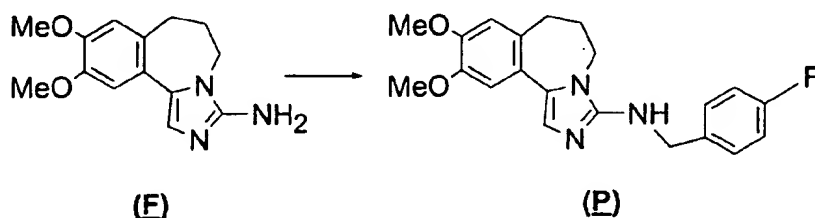
Example N



10. **Reduction of imine L to amine N.** Compound L is dissolved in MeOH to which one equivalent NaBH₄ is added. The mixture is stirred at room temperature for 1h. H₂O is added to the solution, and the solvent is removed under vacuum. The resultant crude product is dissolved in CH₂Cl₂ and washed with 5% aqueous NaHCO₃ and H₂O. The organic layer is separated and dried over Na₂SO₄. Evaporation of the solvent gives compound N.

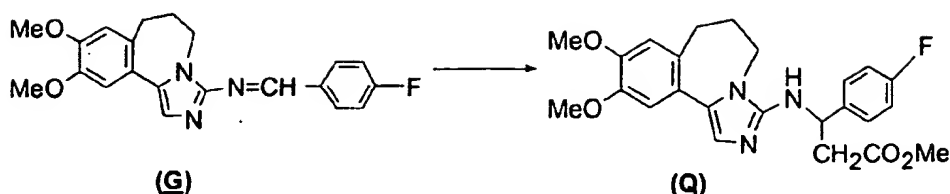
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Example P



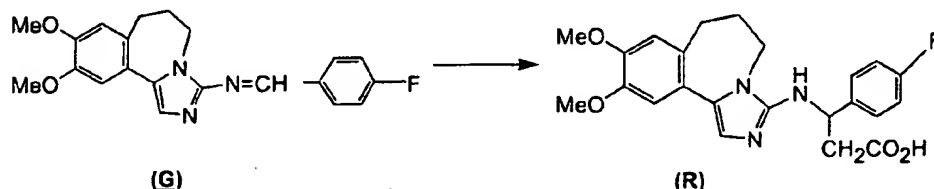
20 **Reductive alkylation.** Excess amount of 4-F-benzaldehyde (more than two equivalents) is added to a suspended solution of F (0.47 mmol) in EtOH (8 mL). The solution is refluxed for 6 h. The residue is dissolved in MeOH (adding THF to help the solubility if necessary), followed by the addition of NaBH₄ (two equivalents). The solution is stirred at room temperature for 30 min. Evaporation of the solvent provides a residue which is partitioned in CH₂Cl₂/H₂O. The organic extracts are washed with NaHCO₃ (5% aq),
25 brine and dried over Na₂SO₄. The solvent is removed in vacuo to afford compound P. The salt of compound P can be recrystallized from MeOH/Et₂O.

Example Q



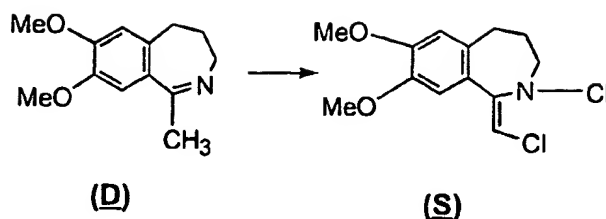
N-[3-(4-F-phenylmethyl) propionate]-6,7-dihydro-9,10-dimethoxyimidazo[5,1-a]benzazepin-3-amine Q. To a solution of lithium diisopropylamine (LDA) (2.0 ml, 3.0 mmol) in THF (5 ml) under N₂ at -78 °C, N-acetyl-2-oxazolidinone (0.323 g, 2.5 mmol) in THF (3 ml) is added dropwise. The mixture is warmed to -15 °C for 1 h and cooled to -78 °C again. Compound G (1.25 mmol) in THF (3 ml) is added dropwise and the mixture is stirred at -78 °C for 2 h (monitored by TLC, CH₂Cl₂/MeOH 9:1). The reaction is quenched by adding 1N HCl in MeOH, and the solvent is removed in vacuo. The residue is then partitioned in CH₂Cl₂/5% aqueous NaHCO₃ and the organic phase is washed with 5% NaHCO₃, brine, dried (MgSO₄) and evaporated. Chromatography (CH₂Cl₂/MeOH) gives compound G.

Example R



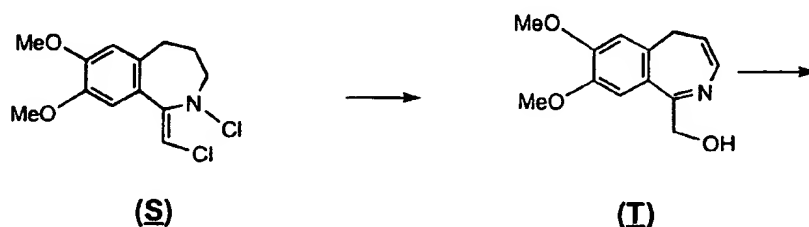
3-(4-F-phenyl)-3-(N-6,7-dihydro-9,10-dimethoxyimidazo[5,1-a]benzazepin)-amino propionic acid hydrochloride R. To a solution of LDA (2.0 ml, 3.0 mmol) in dry THF (5 ml) under N₂ at -78 °C, N-acetyl-2-oxazolidinone (0.323 g, 2.5 mmol) in THF (3 ml) is added dropwise. The mixture is warmed to -15 °C for 1 h and cooled to -78 °C again. Compound G (1.25 mmol) in THF (3 ml) is added dropwise and the mixture is stirred at -78 °C for 2 h (monitored by TLC, CH₂Cl₂/MeOH 9:1). The reaction is quenched by adding 1N aqueous HCl, and the solvent is removed in vacuo. The residue is partitioned in CH₂Cl₂/5% aqueous NaHCO₃, and the organic phase is washed with 5% NaHCO₃, brine, dried (MgSO₄) and evaporated. Chromatography (CH₂Cl₂ / MeOH) gives compound R.

Example S



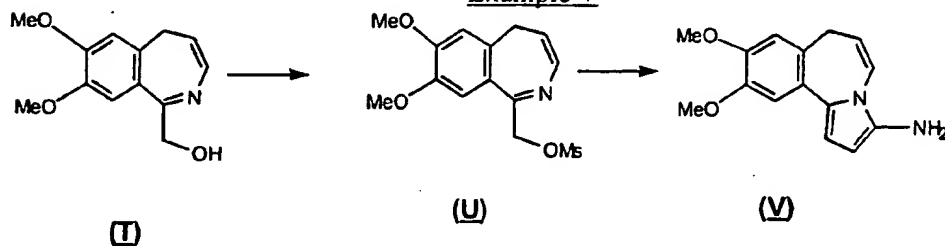
Dichloronation of imine D. In a 25 ml single neck round bottom flask equipped with a magnetic stir bar, rubber septum and N₂ inlet is placed 1g of D under N₂. 12 ml of CH₂Cl₂ is added; the reaction is cooled to -5 °C using an ice/acetone bath, and 1.1 ml of *t*-butyl hypochlorite is added dropwise. The reaction is complete in 15 minutes according to TLC. The reaction product is evaporated in vacuo, and the residue is purified by silica gel chromatography using neat CH₂Cl₂ as eluting solvent. Compound S is obtained from the column.

Example T



In a single neck 50 ml round bottom flask equipped with a magnetic stir bar and water condenser is placed 72 mg of NaOH in 12 ml H₂O. This is heated to reflux; then 500 mg of S is taken up in 10 ml of dioxane and added to the flask. The reaction solution is refluxed for 3 hours and evaporated in vacuo. The resultant residue is purified by chromatography to afford compound T.

Example V



9,10-Dimethoxy-imidazo[5,1-a]benzazepin-3-amine V. To a solution of compound T in CH₂Cl₂, 1 equivalent of Et₃N is added. After the solution is stirred at room temperature for 5 min, one equivalent of methyl-sulfonyl (Ms) chloride is added dropwise. The reaction is complete in 1 hour. The solution then is diluted with more

CH₂Cl₂ and washed with H₂O and brine. The organic layer is separated and dried over Na₂SO₄. Removal of the solvent gives U as a residue. In a separate flask is placed NaOH solution; then Na₂NCN is added along with EtOH. This is heated to reflux. Residue U is dissolved in EtOH and added to the reaction. After refluxing for 3 hours,
5 the reaction is complete. Removal of the solvent provides a crude product which is purified by silica gel column to give compound V.

Compositions of the Invention

A composition of the subject invention comprises:

- 10 a) a safe and effective amount of a compound of the invention; and
b) a pharmaceutically-acceptable excipient.

Typically, such composition comprises several excipients. It may also optionally comprise other active compounds which do not substantially interfere with the activity of the subject invention compound.

15 The compositions of the subject invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical or parenteral administration. Compositions of the subject invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a subject compound that is suitable for administration to a human or lower animal subject, in a single dose, according to good
20 medical practice.

As used herein, a "safe and effective amount" of a subject compound is an amount large enough to significantly induce a positive modification in the symptoms and/or condition to be treated in a host, but small enough to avoid serious adverse side effects in the host (such as toxicity, irritation, or allergic response), commensurate with a reasonable
25 benefit/risk ratio. The safe and effective amount will vary with such factors as the particular condition being treated, the age and physical condition of the patient, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form to be used, and the dosage regimen employed.

The term "pharmaceutically-acceptable excipient", as used herein, includes
30 physiologically inert, pharmacologically inactive substances which are compatible with the physical and chemical characteristics of the subject invention compound used, and which are of sufficiently high purity and sufficiently low toxicity to be suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the

excipients of the subject composition are capable of being commingled with the subject invention compound, and with each other in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the compound, under ordinary use situations.

5 Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable excipients well-known in the art may be used. Excipients include, but are not limited to, polymers, resins, plasticizers, fillers, binders, lubricants, glidants, disintegrants, solvents, co-solvents, buffer systems, surfactants, preservatives, sweetening agents, flavoring agents, and dyes or pigments. The amount of excipients
10 employed in conjunction with the subject compound is sufficient to provide a practical quantity of material for administration per unit dose of the subject compound.

Some examples of substances which can serve as pharmaceutically-acceptable excipients are sugars, such as lactose, dextrose, glucose and sucrose; starches, such as cornstarch and potato starch; cellulose and its derivatives, such as methylcellulose, sodium
15 carboxymethylcellulose, ethylcellulose, hydroxypropylcellulose and cellulose acetate; polymers, such as povidone and carbomers; powdered tragacanth; gums, such as xanthan, guar and acacia; malt; solid lubricants, such as stearic acid, magnesium stearate, and talc; inorganic fillers, such as calcium phosphates and calcium sulfate; disintegrants, such as sodium starch glycolate, croscarmellose sodium, and microcrystalline
20 cellulose; encapsulating and coating materials, such as gelatins, waxes, and cellulose derivatives; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of the obroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; alginic acid; surfactants such as the Tweens®, alkyl sulfate salts, salts of fatty acids, sucrose esters; ethyl oleate; coloring agents; flavoring agents; tableting
25 agents; stabilizers; antioxidants; preservatives; solvents, such as ethanol, pyrogen-free water; isotonic saline; and buffer solutions, such as phosphoric, tartaric, citric, and acetic acids, and their sodium, potassium, and ammonium salts.

Preferred compositions of the subject invention are oral dosage forms. The term
30 "oral dosage form", as used herein, means any pharmaceutical composition intended to be systemically administered to an individual by delivering the composition via the mouth to the gastrointestinal tract of an individual. Preferred are oral unit dosage forms, such as tablets, coated or non-coated, and capsules, hard or soft gel. Subject oral unit dosage form

compositions comprise preferably at least about 4 mg, more preferably at least about 20 mg, more preferably still at least about 100 mg, and preferably at most about 1000 mg, more preferably at most about 500 mg, more preferably still at most about 250 mg, of a subject compound. Subject oral dosage form compositions comprise preferably at least about 1%,
5 more preferably at least about 10%, and preferably at most about 70%, more preferably at most about 40%, of a subject compound; and comprise preferably at least about 30%, more preferably at least about 60%, and preferably at most about 99%, more preferably at most about 90%, pharmaceutically-acceptable excipients.

Parenteral dosage forms are also preferred subject invention compositions. The term
10 "parenteral dosage form", as used herein, means any pharmaceutical composition intended to be systemically administered to a human or lower animal via delivery of a solution or emulsion containing the active ingredient, by puncturing the skin of the individual, in order to deliver the solution or emulsion to the circulatory system of the individual either by intravenous, intramuscular, intraperitoneal or subcutaneous injection. Subject parenteral
15 unit dosage form compositions comprise preferably at least about 1 mg, more preferably at least about 6 mg, more preferably still at least about 30 mg, and preferably at most about 400 mg, more preferably at most about 100 mg, more preferably still at most about 40 mg, of a subject compound. Subject parenteral dosage form compositions comprise preferably at least about 1%, more preferably at least about 5%, and preferably at most about 20%,
20 more preferably at most about 10%, of a subject compound; and comprises preferably at least about 80%, more preferably at least about 90%, and preferably at most about 99%, more preferably at most about 95%, pharmaceutically-acceptable excipients. In addition, dosages for injection may be prepared in dried or lyophilized form. Such forms can be reconstituted with water, saline solution, or a buffer solution, depending on the preparation
25 of the dosage form. Such forms may be packaged as individual dosages or multiple dosages for easier handling. Where lyophilized or dried dosages are used, the reconstituted dosage form is preferably isotonic, and at a physiologically compatible pH, and comprises the subject compound and excipients in the amounts and percentages indicated previously in this paragraph.

30 Methods of Treatment Using the Compounds

Subject invention compounds have demonstrated pharmacological activity in processes known to be associated with one or more of cardiovascular activity, inflammatory

mechanisms, oncology, and regulation of protein transport from cells. The subject invention includes methods of using the above compounds of the subject invention for therapeutic or preventative treatment of one or more of the following diseases or disorders: congestive heart failure, arrhythmia, hypotension, cardiac reperfusion injury, arteriosclerosis, restenosis, vascular tone, bacterial infection, cancer, Kaposi's sarcoma, psoriasis, migraine, nasal congestion, allergic responses, rheumatoid arthritis, and osteoporosis. Such methods comprise administering to a human or lower animal in need of such treatment or prevention a safe and effective amount of a subject invention compound.

For preferred oral administration of compounds and/or compositions of the subject invention, preferably at least about 0.1 mg/kg, more preferably at least about 0.5 mg/kg, more preferably still at least about 2 mg/kg, and preferably at most about 20 mg/kg, more preferably at most about 5 mg/kg, more preferably still at most about 2 mg/kg, of a subject compound is administered to a human or lower animal, preferably at least about 1 time, more preferably at least about 2 times, and preferably at most about 4 times, more preferably at most about 2 times, daily. Treatment duration using such oral daily dosages is dependent on the disease or disorder being treated; it is preferably at least about 1 day, more preferably at least about 3 days, more preferably still at least 7 days, and preferably at most about 5 years, more preferably at most about 60 days, more preferably still at most about 15 days.

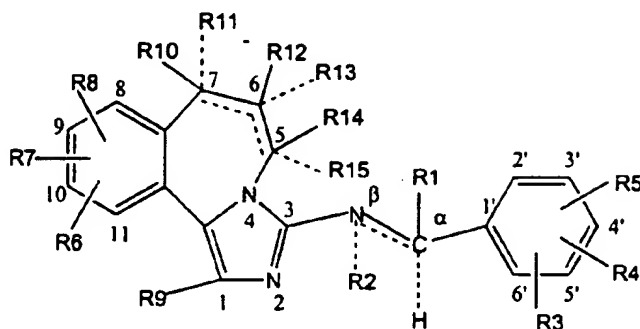
For preferred parenteral administration of compounds and/or compositions of the subject invention, preferably at least about 0.04 mg/kg, more preferably at least about 0.2 mg/kg, more preferably still at least about 1 mg/kg, and preferably at most about 10 mg/kg, more preferably at most about 4 mg/kg, more preferably still at most about 1 mg/kg, of a subject compound is administered to a human or lower animal, preferably at least about 1 time, more preferably at least about 2 times, and preferably at most about 4 times, more preferably at most about 2 times, daily. Treatment duration using such parenteral daily dosages is dependent on the disease or disorder being treated; it is preferably at least about 1 day, more preferably at least about 3 days, more preferably still at least 7 days, and preferably at most about 60 days, more preferably at most about 20 days, more preferably still at most about 5 days.

While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the arts that various changes and modifications of the

subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

What is claimed is:

1. A compound having the structure:



wherein:

- (a) The bond between C_{α} and N_{β} is a single bond, or a double bond whereby R_2 (and H on C_{α}) are nil;
- (b) the bond between C_5 and C_6 is a single bond, or a double bond whereby R_{13} and R_{15} are nil; the bond between C_6 and C_7 is a single bond, or a double bond whereby R_{11} and R_{13} are nil; but the C_5-C_6 and C_6-C_7 bonds are not both double bonds;
- (c) R_1 is selected from hydrogen, alkyl, aryl, and heterocycle;
- (d) R_2 , if not nil, is selected from hydrogen, alkyl, alkylacyl, arylacyl, alkylsulfonyl, and arylsulfonyl;
- (e) R_3 , R_4 and R_5 are each independently selected from hydrogen, halo, alkyl, aryl, heterocycle, nitro, cyano, and unsubstituted or alkyl- or aryl- or heterocycle-substituted hydroxy, thio, amino, amide, formyl (acyl), carboxy, and carboxamide; or R_3 and R_4 together are alkylene or heteroalkylene attached to adjacent carbons of the phenyl to which R_3 and R_4 are attached, and R_5 is as specified in (e) above;
- (f) R_6 , R_7 and R_8 are each independently selected from hydrogen, halo, alkyl, aryl, heterocycle, nitro, cyano, and unsubstituted or alkyl- or aryl- or heterocycle-substituted hydroxy, thio, amino, amide, sulfonamide, formyl (acyl), carboxy, and carboxamide; or R_6 and R_7 together are alkylene or

heteroalkylene attached to adjacent carbons of the phenyl to which R6 and R7 are attached, and R8 is as specified in (f) above;

- (g) R9 is selected from hydrogen, halo, alkyl, aryl, heterocycle, and carboxy and its alkyl and aryl esters and amides;
- (h) R10, R12 and R14, and R11, R13 and R15 if not nil, are each independently selected from hydrogen, alkyl, and aryl;

and an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof.

2. The compound of Claim 1 wherein:

- (a) R1 is selected from hydrogen; linear, branched and cyclic alkanyl and alkenyl; and phenyl; preferably from unsubstituted C₁-C₆ linear, or C₃-C₆ branched or cyclic, alkanyl; or unsubstituted C₂-C₆ linear, or C₃-C₆ branched or cyclic, alkenyl having one double bond;
- (b) R2, if not nil, is selected hydrogen; linear, branched and cyclic alkanyl and alkenyl; alkylacetyl, and phenylacetyl; preferably from hydrogen; unsubstituted C₁-C₆ linear, or C₃-C₆ branched or cyclic, alkanyl; or unsubstituted C₂-C₆ linear, or C₃-C₆ branched or cyclic, alkenyl having one double bond;
- (c) R3, R4, and R5 are each independently selected from hydrogen, halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacetyl, arylacetyl, carboxy and its alkyl and aryl esters and amides; or R3 and R4 together are alkylene or heteroalkylene and, with the carbons to which they are attached, are cycloalkyl, aryl or heterocycle ring, and R5 is hydrogen; preferably from hydrogen, halo, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, thio, C₁-C₄ alkylthio, C₁-C₄ mono- or dialkylamino, C₁-C₄ alkylacetyl;
- (d) R6, R7, and R8 are each independently selected from hydrogen, halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, sulfonamide, alkylsulfonamide, arylsulfonamide, formyl, alkylacetyl, arylacetyl, carboxy and its alkyl and aryl esters and amides; or R6 and R7 together are alkylene or

heteroalkylene and, with the carbons to which they are attached, are cycloalkyl, aryl or heterocycle ring, and R8 is hydrogen; preferably one of R6 and R7 is bonded at the 8 position, the other at the 9 position, of the fused rings; R6 is selected from alkoxy, alkylthio, monoalkylamino, dialkylamino, the alkyl portions thereof being saturated and unsubstituted and having from 1 to 4 carbon atoms; R7 is selected from hydrogen, alkoxy, alkylthio, monoalkylamino, dialkylamino, the alkyl portions thereof being saturated and unsubstituted and having from 1 to 4 carbon atoms; or the alkyl portions of R6 and R7 are connected forming an alkylene moiety of from 1 to 4 carbon atoms; R8 is hydrogen.

- (e) preferably R9 is selected from hydrogen, halo, C₁-C₄ alkyl, and phenyl;
- (f) preferably R10, R12 and R14, and R11, R13 and R15 if they exist, are each independently hydrogen or C₁-C₄ alkyl.

3. The compound of Claim 1 or 2 wherein R2, R10, R12 and R14, and R11, R13 and R15 if they exist, are all hydrogen.
4. The compound of any of Claims 1-3 wherein R6 and R7 are both C₁-C₄ alkoxy or C₁-C₄ alkylthio, preferably both are methoxy.
5. The compound of any of Claims 1-4 wherein the C_α-N_β bond is a single bond, and preferably the C₅-C₆ and C₆-C₇ bonds are both single bonds.
6. The compound of any of Claims 1-5 wherein R1 is methyl; and preferably R3, R4 and R5 are selected from: from one to three of R3, R4 and R5 being independently selected from F, Cl and Br, the other(s) being hydrogen; from one to three of R3, R4 and R5 being independently unsubstituted methyl or unsubstituted methoxy, the other(s) being hydrogen; and one or two of R3, R4 and R5 being independently trifluoromethyl or trifluoromethoxy, the other(s) being hydrogen or fluoro.

7. A composition comprising:
 - (a) a safe and effective amount of a compound of any of Claims 1-6; and
 - (b) a pharmaceutically-acceptable excipient.
8. A method for treating or preventing congestive heart failure, hypotension, cardiac arrhythmia, or cardiac reperfusion injury comprising administering to a human or lower animal in need thereof a safe and effective amount of a compound of any of Claims 1-6.
9. A method for treating or preventing a disease or disorder caused by cellular protein transport including, but not limited to, osteoporosis, rheumatoid arthritis, allergic responses, restenosis, vascular tone, cancer, Kaposi's sarcoma, psoriasis, and bacterial infections, comprising administering to a human or lower animal in need thereof a safe and effective amount of a compound of any of Claims 1-6.
10. A method for treating or preventing nasal congestion or migraine comprising administering to a human or lower animal in need thereof a safe and effective amount of a compound of any of Claims 1-6.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/23153

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 917 610 A (K. TAKACS ET AL.) 4 November 1975 (1975-11-04) cited in the application claims 1-19	1-10
A	US 4 143 143 A (M.-P. SEILER) 6 March 1979 (1979-03-06) cited in the application claims 1-14	1-10

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

Special categories of cited documents:

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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17 December 1999

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/23153

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